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SUPPLEMENT ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Biological and technical complications of tilted implants in comparison with straight implants supporting fixed dental prostheses. A systematic review and meta-analysis

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Abstract

Objectives: To evaluate the implant failure, marginal bone loss (MBL), and other biological or technical complications of restorations supported by tilted and straight implants after at least 3 years in function.

Methods: Electronic and manual searches were performed in MEDLINE, Embase, Web of Science, and OpenGrey to identify clinical studies published up to December 2017. After duplicate study selection and data extraction, the risk of bias was assessed with the ROBINS-I tool. Random-effects meta-analyses of relative risks (RRs) or mean differences (MD) and their 95% confidence intervals (CIs) were performed, followed by subgroup/sensitivity analyses and application of the GRADE approach.

Results: A total of 17 nonrandomized studies (eight prospective/nine retrospective) were included. The number of implants of the overall systematic review was 7,568 implants placed in 1,849 patients supporting either full-arch or partial implant prostheses. No difference in the failure of tilted and straight implants was seen (eight studies; 4,436 implants; RR = 0.95; 95% CI = 0.70 to 1.28; p = 0.74), with the quality of evidence being very low due to bias and imprecision. Likewise, no difference in MBL was seen between tilted and straight implants (16 studies; 5,293 implants; MD = 0.03 mm; 95% CI = −0.03 to 0.10 mm; p = 0.32), with the quality of evidence being very low due to bias and inconsistency. Contradictory results regarding implant survival were found from prospective and retrospective studies, which could indicate bias from the latter.

Conclusions: Within the limitations of the present systematic review, no effect of implant inclination on implant survival or peri-implant bone loss was found.

KEYWORDS
axial load, complications, fixed dental prostheses, fixed dental prosthesis, implant dentistry, nonaxial load, prosthetic dentistry, systematic review

1 | INTRODUCTION

1.1 | Rationale

Various types of implant-supported restorations have emerged as an effective solution for partial or total edentulousness, bolstered by clinical evidence supporting their excellent longevity (Pjetursson & Lang, 2008; Pjetursson, Thoma, Jung, Zwahlen & Zembic, 2012; Pjetursson, Zwahlen & Lang, 2012). In particular, restorations like conventional bridgework on dental implants (Pjetursson et al., 2004), mixed tooth-and-implant supported reconstructions (Lang et al., 2004), and single crowns on implants (Jung et al., 2008) have been analyzed after at least 5 years in function and given satisfying results. However, all previous evaluations were based on the assumption that the implants were placed and loaded in an axial direction.

Implants that are placed in a nonaxial direction (i.e., tilted implants) might be considered in many cases and for a variety of reasons. Tilted implants might be indicated in order to avoid damage to important anatomical structures, to avoid bone augmentation procedures of severely resorbed jaws and sinus lift procedures, or to allow the placement of longer implants with increased bone-to-implant contact. In addition, tilted implants might facilitate a wider distance between anterior–posterior implants and better load distribution or eliminate the use of cantilevers. Some in silico studies have indicated that tilted implants might react more favorably compared to straight implants from a biomechanical point of view (Bellini, Romeo, Galbusera, Agliardi et al., 2009; Bellini, Romeo, Galbusera, Taschieri et al., 2009), although contradictory results exist (Lan, Pan, Lee, Huang & Wang, 2010). However, clinical recommendations for the use of tilted implants have to be based on robust clinical evidence with an adequate follow-up period.

Previous meta-analyses on restorations supported by tilted and straight implants (Chrcanovic, Albrektsson & Wennerberg, 2015; Del Fabbro & Ceresoli, 2014; Monje, Chan, Suarez, Galindo-Moreno & Wang, 2012) focused on their short-term performance after 1 year of follow-up, were not registered a priori (Sideri, Papageorgiou & Eliades, 2018), used outdated meta-analytic methods (Veroniki et al., 2016), and did not judge the strength of their clinical recommendations with the Grades of Recommendations, Assessment, Development, and Evaluation (GRADE) approach (Guyatt et al., 2008).

1.2 | Objective

The objective of the present systematic review was to answer the following focused question: "what is the rate of biological complications, technical complications, and patient-reported outcome measures (PROMs) among partially/fully edentulous adult patients treated with tilted and straight implants after at least 3 years of function?"

2 | MATERIAL AND METHODS

2.1 | Protocol and registration

The present review was performed and reported according to the Cochrane Handbook (Higgins & Green, 2011) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati et al., 2009), respectively. The present review was registered a priori in PROSPERO (CRD42018086593).

2.2 | Eligibility criteria

Based on the Participants, Intervention, Comparison, Outcome, Study design (PICOS) structure, this translated to:

- Population: partial or fully edentulous adult patients;
- Intervention: tilted implants supporting fixed dental prostheses (FDPs);
- Comparison: straight implants supporting FDPs;
- Outcome: biologic complications, technical complications, and PROMs after at least 3 years of function;
- Study design: randomized or nonrandomized comparative clinical studies in humans.

The inclusion criteria in detail included randomized clinical trial and nonrandomized clinical studies with a minimum mean follow-up of 3 years that presented data on prosthetic treatment and biological complications thereof. Excluded were studies with mean follow-up <3 years, sample size <20 patients, studies on zygomatic or trans-sinus implants, nonclinical studies, reviews, letters to editors, technical notes, and position papers.

2.3 | Information sources and searches

An electronic search was performed in duplicate by two authors (KAAA, DSP) in Medline (via PubMed), Embase, and Web of Science for studies published in English up to December 2017 without any time restriction (). MeSH (Medical Subject Headings), EMTREE, and "free-text" terms were employed and combined with the Boolean operators OR, AND. In addition, the System for Information on Grey Literature in Europe (SIGLE) database was searched through http://www.opengrey.eu, and a manual search of all issues since 2000 of several implant-related journals was performed in duplicate (KAAA, YN): Clinical Oral Implants Research, Clinical Implant Dentistry and Related Research, European Journal of Oral Implantology, Implant Dentistry, International Journal of Oral and Maxillofacial Surgery, Journal of Clinical Periodontology, Journal of Dental Research, Journal of Oral and Maxillofacial Surgery, Journal of Oral Implantology, Journal of Periodontology, The International Journal of Oral and Maxillofacial Implants, The International Journal of Periodontics and Restorative Dentistry, The International Journal of Prosthodontics, and The Journal of Prosthetic Dentistry. At last, the reference lists of included studies were checked in duplicate (KAAA, DSP) to identify additional records.

2.4 | Study selection

After removal of duplicate reports, the potentially eligible titles and abstracts were screened by two reviewers (KAAA, DSP). In a second phase, the relevant titles were obtained and assessed by reading the full text in duplicate (KAAA, DSP). During this stage, the articles that were judged to contain all the inclusion criteria in full were identified. Disagreements between the two authors were solved by discussion with a third reviewer (DB), and agreement was quantified with a kappa statistic.

2.5 | Data collection process and data items

Two authors (KAAA and DSP) performed data extraction in duplicate using Excel® (Microsoft Office 2017, Redmond, WA, USA) spreadsheets, with disagreements being resolved by discussion with a third reviewer (DB). The following data were extracted from each included study: authors and publication year, study design, sample size, implant system, number of implants placed (total, tilted, and straight), implant location, surgical techniques applied, amount of implant angulation, number of implants within the prosthesis, type of prosthetic restoration (fixed full-arch, partial), loading time, and study follow-up (years).

The primary outcome of the present review was the biological complication of implant failure, as this is the most objective outcome that is directly relevant to the patient. The main secondary outcome was peri-implant marginal bone loss (MBL) assessed radiographically in mm, as this is linked to peri-implant disease and implant prognosis. The dental implant was considered as statistical unit in all cases.

In addition, the outcomes of mucositis or peri-implantitis were included as secondary outcomes, using the case definitions of mucositis and peri-implantitis defined in the AAP/EFP World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions held in November 2017 in Chicago (Heitz-Mayfield & Salvi, 2018; Schwarz, Derks, Monje & Wang, 2018).

At last, prosthetic complications comparing prostheses solely supported by straight implants to the ones supported by straight and tilted implants and PROMs were included on patient level and assessed in a descriptive manner.

2.6 | Risk of bias in individual studies

The risk of bias of randomized trials was planned to be assessed with the Cochrane Risk of Bias (RoB) tool 2.0 (Higgins et al., 2016), but no such trials were identified. The risk of bias of nonrandomized studies was evaluated in duplicate by two authors (KAAA and DSP) using the ROBINS-I tool (Sterne et al., 2016). This assesses risk of bias in seven domains: (a) confounding, (b) selection of participants into the study, (c) classification of interventions, deviations from intended interventions, (d) to missing data, (e) measurement of outcomes, and (f) bias in selection of the reported result. The risk of bias judgments at domain or study is finally interpreted as follows:

- Low risk of bias—The study is judged to be at low risk of bias for all domains.
- Moderate risk of bias—The study is judged to be at low or moderate risk of bias for all domains.
- Serious risk of bias—The study is judged to be at serious risk of bias in at least one domain, but not at critical risk of bias in any domain.
- Critical risk of bias—The study is judged to be at critical risk of bias in at least one domain.
- No information—There is no clear indication that the study is at serious or critical risk of bias, and there is a lack of information in one or more key domains of bias.

2.7 | Summary measures and synthesis of results

For this review, the primary outcome was implant failure for any reason, while the secondary outcome was peri-implant MBL measured radiographically in mm. Relative risks (RRs) for implant failure or mean differences (MD) for MBL with the corresponding 95% confidence intervals (CIs) were chosen as effect measures.

As implant failure and MBL might be affected by various patient-, implant-, surgery-, or restoration-related characteristics, a wide variation of true effects was expected and a random-effects model was judged a priori sensible, based on biological, clinical, and statistical grounds (Papageorgiou, 2014a). Instead of the traditional estimator method (DerSimonian & Laird, 1986), the Paule–Mandel estimator was used due to improved performance (Veroniki et al., 2016).

The extent and impact of between-study heterogeneity were assessed by inspecting the forest plots and calculating the τ^2 and the I^2, respectively; I^2 defines the proportion of total variability in the result explained by heterogeneity, and not chance (Higgins, Thompson, Deeks & Altman, 2003). Heterogeneity was roughly categorized as low, moderate, and high to I^2 values of 25%, 50%, and 75% (Higgins et al., 2003), although the heterogeneity's localization on the forest plot was also judged. In addition, the 95% CIs around τ^2 and I^2 were calculated (Ioannidis, Patsopoulos & Evangelou, 2007) to quantify our uncertainty around these estimates. Ninety-five percent predictive intervals were calculated for meta-analyses of ≥3 trials to incorporate existing heterogeneity and provide a range of possible effects for a future clinical setting (IntHout, Ioannidis, Rovers & Goeman, 2016). All analyses were conducted in Stata SE version 14.2 (StataCorp LP, College Station, TX, USA) by one author (SNP), and the dataset was made openly available (Apaza Alccayhuaman et al., 2018). A two-sided $p \le 0.05$ was considered significant for hypothesis testing, except for $p \le 0.10$ used for tests of between-studies or between-subgroups heterogeneity (Ioannidis, 2008).

2.8 | Additional analyses and risk of bias across studies

Possible sources of heterogeneity were sought through random-effects subgroup analyses for meta-analyses of ≥5 studies according to: follow-up (3 or 5 years), jaw (maxilla or mandible), restoration type (full-arch or partial denture), and loading timing (immediate or delayed). Indications of reporting biases (including small-study effects and publication bias) were assessed with Egger's linear regression test (Egger, Davey Smith, Schneider & Minder, 1997) and contour-enhanced funnel plots, for meta-analyses with ≥10 studies.

Robustness of the results was checked with sensitivity analyses based on the inclusion of (i) randomized or nonrandomized studies, (ii) prospective or retrospective studies, and (iii) small or large studies (arbitrarily judged as having ≥100 tilted implants), as these might introduce bias (Cappelleri et al., 1996; Papageorgiou, Kloukos, Petridis & Pandis, 2015a; Papageorgiou, Xavier & Cobourne, 2015).

The overall quality of meta-evidence (i.e., the strength of clinical recommendations) was rated using the Grades of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, as very low, low, moderate, or high (Guyatt et al., 2008) and Summary of Findings tables were constructed using the improved format proposed by Carrasco-Labra et al. (2016) and recent guidance on incorporating nonrandomized studies (Schünemann et al., 2018). The minimal clinical important (Norman, Sloan & Wyrwich, 2003), large, and very large effects were defined as half, one, and two standard deviations (using the average standard deviation for straight implants across included studies), respectively. Cutoffs of 1.5, 2.0, and 5.0 were adopted for RR according to the GRADE guidelines (Schünemann, Brozek & Oxman, 2009). The produced forest plots were augmented with contours denoting the magnitude of the observed effects (Papageorgiou, 2014b) to assess heterogeneity, clinical relevance, and imprecision.

3 | RESULTS

3.1 | Study selection

The electronic search yielded a total of 794 titles (Figure 1), while no new references were found through hand searching. After removal of duplicates, 661 articles were screened, from which 564 were excluded by both reviewers. The full-text assessment of the remaining 97 papers resulted in the exclusion of 75 more papers for various reasons and 17 articles were finally included in this systematic review (Figure 1;). The agreement between the two reviewers

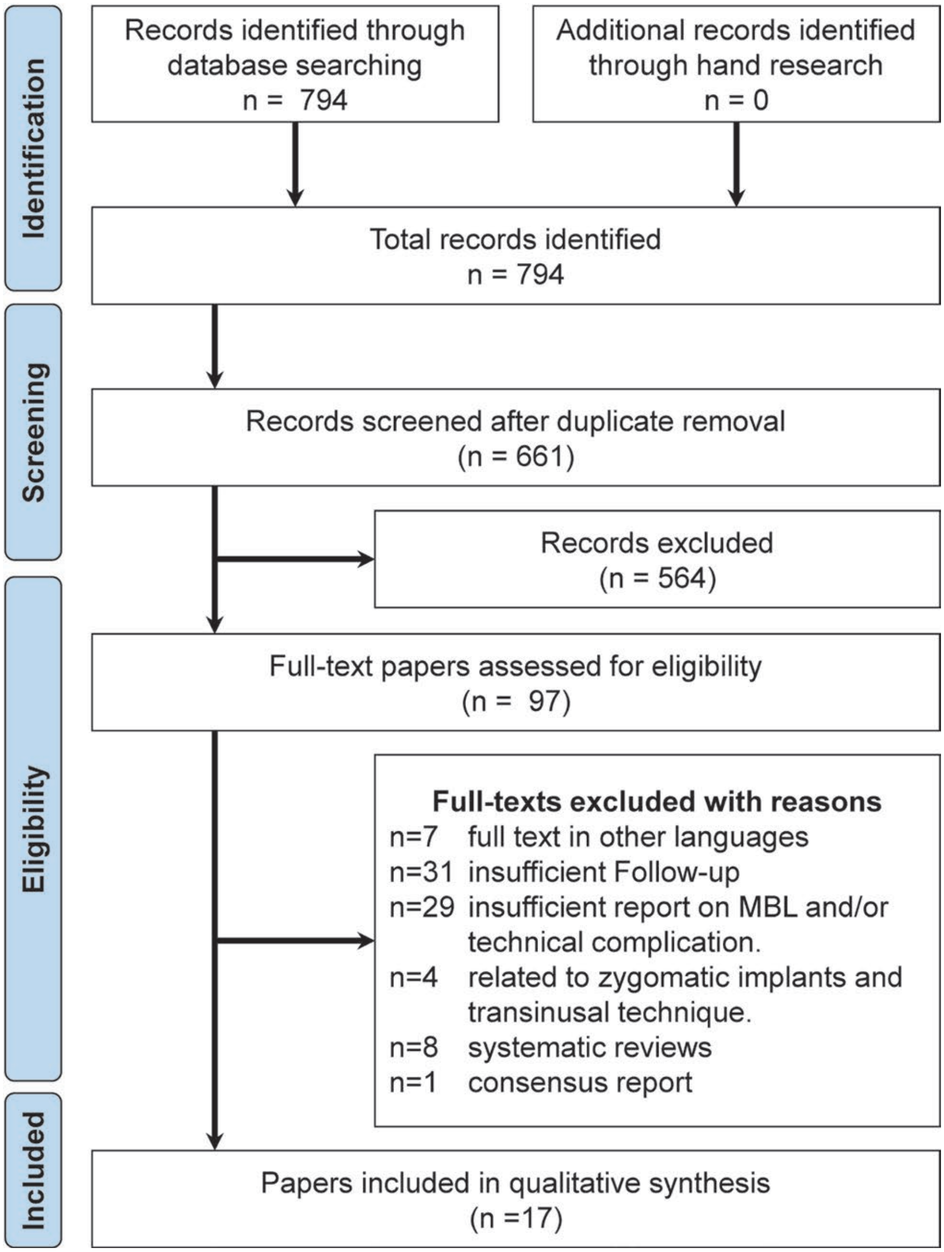

FIGURE 1 PRISMA flow diagram for the identification and selection of studies

was almost perfect (κ = 0.91). In addition, raw data were provided in tabular form in one included study (Barnea et al., 2016), which were extracted and reanalyzed.

3.2 | Study characteristics

The 17 included studies were published between 2001 and 2017, with the majority being published in the last 5 years (Table 1). Four studies included partial FDPs and 13 full-arch FDPs, while no studies related to single crown supported by tilted implants were found. No randomized clinical trials could be identified; about half of included studies (*n* = 8; 47%) were prospective and the rest (*n* = 9; 53%) were retrospective nonrandomized comparative studies. These 17 studies reported on 1,584 patients receiving 6,202 implants of six different systems, although one implant system was used in the majority of the studies (*n* = 11; 65%). Most studies were small to moderate in terms of sample size (median of 36 patients per study), with only three studies presenting large cohorts exceeding 100 patients (and six studies having more than 100 tilted implants). The surgical techniques applied included guided implant placement in four (24%) of the included studies. The angulation of the tilted implants ranged between 15 and 50 degrees (Table 2).

3.3 | Risk of bias within studies

Assessment of the risk of bias of included studies with the ROBINS-I tool indicated that only three studies (18%) presented moderate risk of bias, while the majority of the studies (*n* = 14; 82%) were in serious risk of bias (Figure 2). The most problematic domains of the ROBINS-I tool were related to confounding (serious in 71% of the studies) followed by outcome measurement (serious in 47% of the studies), selection of the participants into the study (high risk in 12% of the studies), and missing data (high risk in 12% of the studies).

3.4 | Results of individual studies

3.4.1 | Biological complications

As far as the primary outcome of implant survival is concerned, very high % survival rates were seen for both tilted implants (95.0%–100%) and straight implants (87.5%–100%) with limited variation between tilted-straight implants or between 3 and 10 years of follow-up (Table 3). As far as the secondary outcome of MBL is concerned, greater variability was seen with mean MBL for tilted implants ranging between 0.4 and 2.0 mm and mean MBL for straight implants ranging between 0.5 and 1.9 mm (Table 4). Apart from aggregate data provided by most studies, one study (Barnea et al., 2016) also provided raw data that were reanalyzed. The results indicated that no difference in overall MBL was seen between tilted and axial implants after 3, 5, or 10 years of follow-up (). However, the extent of angulation for the tilted implants was significantly associated with MBL, with an additional 0.6 mm of MBL being seen for every additional 10° of implant tilting ().

By bad luck, no uniform data were provided on inflammatory parameters of the peri-implant tissues, rendering it impossible to classify correctly peri-implant mucositis or peri-implantitis. Only nine studies elaborated on peri-implant pathology, two of which were using peri-implant mucositis as classification and five studies classified the complications as peri-implantitis. In only one study did the authors adopt a systematic and appropriate classification for peri-implantitis (Francetti, Romeo, Corbella, Taschieri & Del Fabbro, 2012), where it was reported that 7% of the implants in 4.3% of the patients exhibited peri-implantitis (all of them pertaining to straight implants).

3.4.2 | Technical complications

From most included studies, it was not possible to retrieve data comparing technical complications separately for tilted and straight implants, as patients mostly received restorations supported by a combination of straight and tilted implants and reported complications on the restoration level.

In one FDP study (Queridinha, Almeida, Felino, de Araújo Nobre & Maló, 2016), the outcome of partial FDPs supported by either two axial implants or one axial and one tilted implants were compared. In another study (Krennmair et al., 2016), full-arch FDPs supported by either four axial implants or two axial and two distally tilted implants were also compared. Both studies reported technical complications at level of the prosthetic restorations with no significant differences between the two groups. However, it was not reported if the complications occurred at the axial or tilted implants so that a comparison was not possible.

3.4.3 | PROMs

Only two studies (Agliardi et al., 2014; Di et al., 2013) reported PROMs, which included esthetics, phonetics, function, or comfort and reported excellent results (all >85% in a visual analogue scale) among patients treated with a full-arch restoration integrating tilted and straight implants.

3.5 | Synthesis of results

Quantitative data synthesis was performed in terms of random-effects meta-analyses for the primary and the secondary outcomes of this review (Table 5). As far as the primary outcome of implant failure is concerned, meta-analysis of eight studies and 4436 implants found no significant difference between tilted and straight implants (RR = 0.95; 95% CI = 0.70 to 1.28; $p > 0.05$; Figure 3). However, a wide scattering of studies on both sides of the forest plot with very imprecise estimates was seen (Figure 3), which was probably due to the fact that existing studies had limited samples and moderate follow-ups and therefore few implant failures.

TABLE 1 Demographic data and characteristics of the included studies

Authors	Study type	Patients	Center	No of implants			Implant system	No IMP/FDP	Arch	Restorations	Loading time	Follow-up (years)
				Total	Tilted	Axial						
Agliardi et al. (2014)	pNRS	32	Private rehabilitation center	192	128	64	Nobel Biocare	6	Maxilla	32	Immediate	3
Agnini et al. (2014)	pNRS	30	Foggia University - Italy	202	37	165	Zimmer	4–8	Both	36	Immediate	5
Aparicio et al. (2001)	rNRS	25	Not reported	101	42	59	Nobel Biocare	2–5	Maxilla	29	Delayed	5
Barnea et al. (2016)	rNRS	29	Tel Aviv University	58	29	29	MIS	2	Maxilla	29	Delayed	5
Browayes et al. (2015)	pNRS	20	University Hospital of Ghent, Belgium	80	40	40	Nobel Biocare	4	Both	20	Immediate	3
Crespi, Vinci, Cappare, Romanos and Gherlone (2012)	pNRS	36	San Raffaele Hospital, Milan, Italy	176	88	88	Sweden & Martina	4	Both	44	Mixed	3
Degidi et al. (2010)	pNRS	30	Private dental office, Bologna, Italy	210	120	90	Dentsply	7	Maxilla	30	Immediate	3
Di et al. (2013)	rNRS	69	Implant dentistry Peking University	344	172	172	Nobel Biocare	4	Both	86	Immediate	3
Francetti et al. (2012)	pNRS	47	Two private clinical center	196	98	98	Nobel Biocare	4	Both	49	Immediate	5
Hopp et al. (2017)	rNRS	891	Private Malo clinic Portugal	3564	1782	1782	Nobel Biocare	4	Maxilla	626	Immediate	5
Krennmair et al. (2013)	rNRS	42	University of Vienna	168	84	84	Camlog	4	Mandible	38	Delayed	5
Krennmair et al. (2016)	pNRS	41	University of Vienna	164	40	124	Camlog	4	Mandible	41	Delayed	3
Lopez et al. (2016)	rNRS	111	Private Malo clinic Portugal	532	266	266	Nobel Biocare	4	Both	133	Immediate	7
Malo et al. (2011)	rNRS	35	Private Malo clinic Portugal	84	42	42	Nobel Biocare	2	Both	42	Immediate	8
Malo et al. (2015)	rNRS	324	Private Malo clinic Portugal	1296	648	648	Nobel Biocare	4	Mandible	324	Immediate	3
Pozzi et al. ()	pNRS	27	University of Rome Tor Vergata	81	42	39	Nobel Biocare	4	Maxilla	37	Immediate	3
Queridinha et al. (2016)	rNRS	60	Private Malo clinic Portugal	120	30	90	Nobel Biocare	2	Maxilla	60	Immediate	5

Note.. pNRS, prospective nonrandomized study; rNRS, retrospective nonrandomized study.

TABLE 2 Tilted implant angulation and assessment

Authors	Implant angulation in relation to the vertical axis	Method of measurement	Abutment angulation
Agliardi et al. (2014)	30–45	NR	17–30
Agnini (2014)	20–40	NR	NR
Aparicio (2001)	15–35	NR	30
Barnea et al. (2016)	20–50	Intraoral X-ray	15–25
Browayes (2015)	20–40	NR	30
Crespi et al. (2012)	30–35	NR	30
Degidi (2010)	30–45	NR	NR
Di et al. (2013)	45	NR	17–30
Francetti et al. (2012)	30	NR	30
Hopp (2017)	30–45	NR	30
Krennmair (2013)	0–24 (66–90)	Panoramic X-rays	NR
Krennmair et al. (2016)	NR	NR	20–30
Lopez (2016)	NR	NR	30
Malo (2011)	≤45	NR	NR
Malo (2015)	30 (if ≥45)	NR	30
Pozzi (2012)	25–35	NR	NR
Queridinha et al. (2016)	30–45	NR	30

Note.. NR, not reported.

As far as the secondary outcome of peri-implant MBL is concerned (Table 5), analysis of 16 studies with 5,293 implants found no difference between tilted and straight implants (MD = 0.03 mm; 95% CI = −0.03 to 0.10 mm; $p > 0.05$). Moderate to large heterogeneity could be seen across studies ($I^2 = 73\%$), and studies were scattered across both sides of the forest plot (Figure 4). However, almost all studies pertained to miniscule differences in MBL and therefore were judged to be "noise."

3.6 | Additional analyses and risk of bias across studies

Possible sources of heterogeneity were investigated through subgroup analyses for follow-up (3 vs. 5 years), jaw (maxilla vs. mandible), restoration type (full-arch vs. partial), and loading time (immediate vs. delayed). However, no significant subgroup effects were identified (Table 6).

Reporting biases could not be assessed for implant failure, as <10 studies were included. As far as the outcome of MBL is concerned, both visual inspection of the funnel plot (Figure 5) and Egger's test (coefficient = −0.26; 95% CI = −2.18 to 1.66; $p = 0.78$) indicated no hints of reporting biases.

The robustness of the analyses to possible bias sources was assessed through sensitivity analyses (Table 6). As far as implant failure is concerned, statistically significant differences were seen in sensitivity analyses using the results of either prospective or retrospective studies ($p < 0.10$). Retrospective studies showed that tilted implants had slightly less failure (RR = 0.89), while prospective studies showed considerably more failure (RR = 2.60) compared to straight implants. Even though none of the two subsets was statistically significant, this effect reversal might be interpreted as signs of empirical bias of large magnitude (ratio of RRs of 0.34) originating from retrospective studies. On the other hand, no difference was found in implant failure between small and large studies. At last, the outcome of MBL was affected by neither study design nor study size.

The quality of meta-evidence according to GRADE was found to be very low for both outcomes (Table 7). Starting initially from high, the quality of evidence was downgrade to low for lack of randomization and blinding, and further to very low for methodological limitations, imprecision, and inconsistency. This indicates that future well-controlled studies might probably change the conclusions of the present review.

4 | DISCUSSION

4.1 | Summary of evidence

The present systematic review summarized evidence on the performance of tilted and straight implants in function for at least 3 years. Based on the results of the meta-analyses, no significant difference in implant survival was seen between tilted and straight implants after 3–5 years of function from eight identified studies ($p = 0.74$; Table 5). Both implants had sufficiently high mid-term survival rates that were on average 96.4% for tilted implants and 97.5% after 3–5 years of function (random-effect pooling from the eight studies included in the meta-analyses).

In the same way, for the secondary outcome of peri-implant MBL, no difference was seen between tilted and straight implants

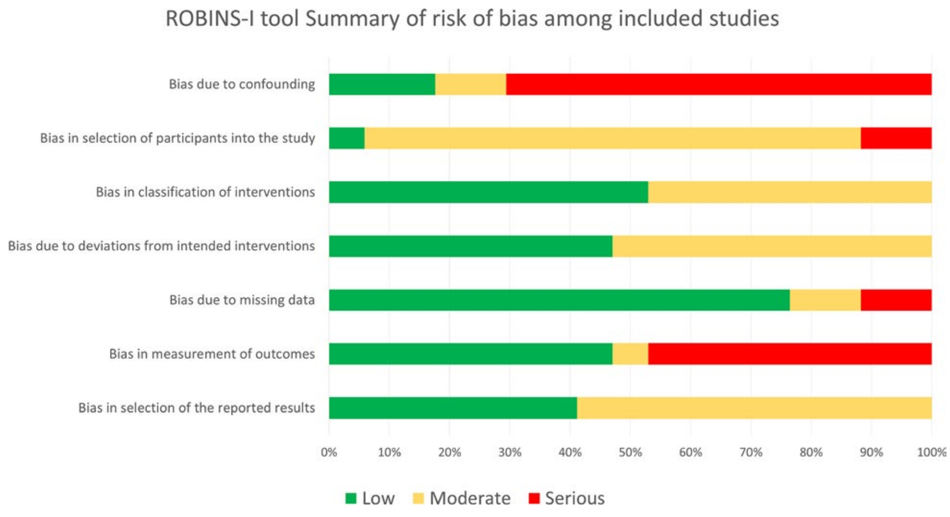

FIGURE 2 Summary risk of bias for the nonrandomized studies included in the systematic review

TABLE 3 Implant failure and % survival rate after 3–10 years of follow-up

Study	FU	Failure		% survival	
		Tilted	Straight	Tilted	Straight
Agliardi et al. (2014)	3	2/128	0/64	98.4	100.0
Agnini (2014)	3	0/24	4/141	100.0	97.2
Aparicio (2001)	3	0/24	2/28	100.0	92.9
Barnea et al. (2016)	3	0/18	0/20	100.0	100.0
Crespi et al. (2012)	3	3/88	0/88	96.6	100.0
Degidi (2010)	3	1/90	1/120	98.9	99.2
Francetti et al. (2012)	3	0/68	0/68	100.0	100.0
Krennmair et al. (2016)	3	0/36	0/112	100.0	100.0
Pozzi (2012)	3	2/40	1/38	95.0	97.4
Francetti et al. (2012)	4	0/48	0/48	100.0	100.0
Agnini (2014)	5	0/2	4/89	100.0	95.5
Aparicio (2001)	5	0/17	2/16	100.0	87.5
Barnea et al. (2016)	5	0/13	0/13	100.0	100.0
Francetti et al. (2012)	5	0/24	0/24	100.0	100.0
Hopp (2017)	5	0/1713	76/1782	96.1	95.7
Krennmair (2013)	5	0/76	0/76	100.0	100.0
Queridinha et al. (2016)	5	0/22	1/70	100.0	98.6
Barnea et al. (2016)	10	0/2	0/2	100.0	100.0

Note.. FU, follow-up in years.

after 3–5 years of function from 16 studies (p = 0.32; Table 5). The pooled MBL for straight implants was found to be 1.10 mm and 1.40 mm after 3 and 5 years of follow-up, respectively (data not shown), which is clinically acceptable according to the Albrektsson and Zarb (Albrektsson & Zarb, 1998) criteria (which allow up to 1.90 and 2.10 mm of MBL for years 3 and 5 of follow-up, respectively). It must be here also stated that only three (18%) of the 17 included studies addressed the issue of biofilm control during follow-up, which is important when interpreting MBL.

It is important to note here that implant tilting entails considerable clinical heterogeneity. First, the definition of the tilted or nonaxially loaded implant is controversial, and usually, implant inclination is evaluated as a mesiodistal angulation in relation to the vertical axis (perpendicular to the occlusal plane). This definition however does not take into account the linguobuccal or palatal–buccal inclination. This needs to be taken into account, as it might have considerable implications for the stability and prognosis of hard and soft peri-implant tissues. In addition, the term "tilted

TABLE 4 Descriptive of marginal bone loss after 3–10 years of follow-up

Study	FU	Tilted implants *n*	Mean	*SD*	Straight implants *n*	Mean	*SD*
Agliardi et al. (2014)	3	126	1.46	0.19	64	1.55	0.31
Agnini (2014)	3	18	1.66	0.16	122	1.58	0.12
Barnea et al. (2016)	3	18	1.18	0.76	20	1.16	0.62
Browaeys (2015)	3	40	1.67	1.22	40	1.55	0.73
Crespi et al. (2012)	3	88	1.11	0.33	88	1.08	0.43
Degidi (2010)	3	120	1.03	0.97	89	0.92	0.89
Di et al. (2013)	3	172	0.80	0.40	172	0.70	0.20
Francetti et al. (2012)	3	68	0.72	0.49	68	0.91	0.50
Krennmair et al. (2016)	3	36	1.40	0.40	112	1.43	0.40
Pozzi (2012)	3	40	0.70	0.27	38	0.50	0.30
Agnini (2014)	4	2	2.00	0.14	58	1.70	0.16
Francetti et al. (2012)	4	48	0.81	0.40	48	0.92	0.55
Agnini (2014)	5	2	2.00	0.14	28	1.73	0.14
Barnea et al. (2016)	5	13	1.50	0.85	13	1.50	0.70
Francetti et al. (2012)	5	24	0.39	0.18	24	0.51	0.17
Hopp (2017)	5	1178	1.19	0.82	1201	1.14	0.71
Krennmair (2013)	5	76	1.24	0.32	76	1.17	0.26
Lopes (2016)	5	190	1.27	1.02	177	1.34	1.10
Malo (2011)	5	17	1.25	0.29	17	1.64	0.63
Malo (2015)	5	470	1.76	1.11	470	1.74	1.11
Queridinha et al. (2016)	5	22	2.02	0.36	70	1.90	0.69
Barnea et al. (2016)	10	2	1.8	0.01	2	1.55	0.28

Note.. FU, follow-up in years; *n*, number of implants; *SD*, standard deviation.

TABLE 5 Random-effects meta-analysis for the primary and secondary outcome and follow-up 3 or 5 years (only the latest follow-up included from each study)

Outcome	Studies (implants)	Effect	95% CI	*p*	Heterogeneity I^2 (95% CI)	τ^2 (95% CI)	95% prediction
Implant failure	8 (4,436)	RR: 0.95	0.70 to 1.28	0.74	0% (0% to 71%)	0 (0 to 2.65)	0.65 to 1.38
Marginal bone loss	16 (5,293)	MD: 0.03 mm	−0.03 to 0.10 mm	0.32	73% (40 to 92%)	0.01 (0 to 0.04)	−0.19 to 0.25 mm

Note.. CI, confidence interval; MD, mean difference; RR, relative risk.

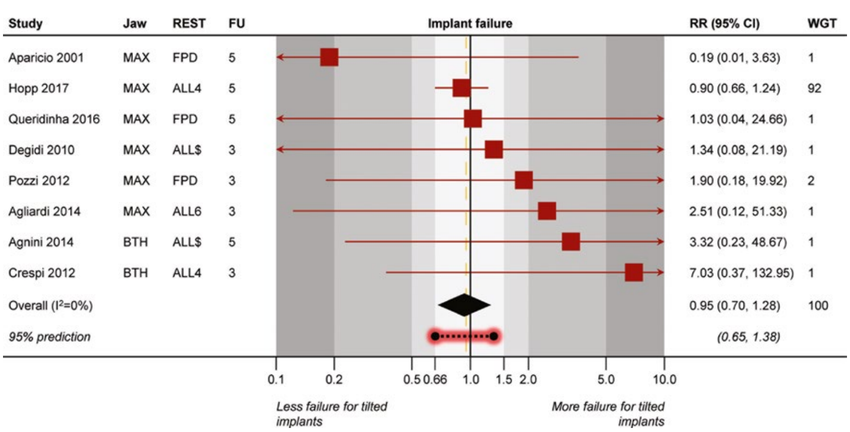

FIGURE 3 Contour-enhanced forest plot for differences in implant failure between tilted and axial implants. *ALL4*, all-on-4; *ALL6*, all-on-6; *ALL$*, all-on-any (full-arch restoration); BTH, both jaws; CI, confidence interval; FPD, fixed partial denture; FU, follow-up in years; MAX, maxilla; REST, restoration; RR, relative risk; WGT, weight

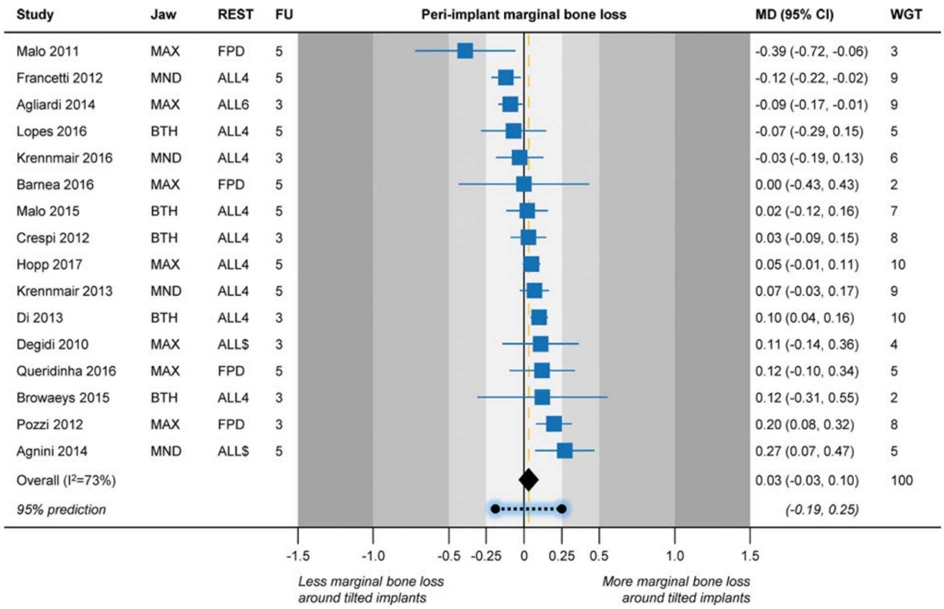

FIGURE 4 Contour-enhanced forest plot for differences in peri-implant marginal bone loss between tilted and axial implants. *ALL4*, all-on-4; *ALL6*, all-on-6; *ALL$*, all-on-any (full-arch restoration); BTH, both jaws; CI, confidence interval; FPD, fixed partial denture; FU, follow-up in years; MAX, maxilla; MD, mean difference; REST, restoration; WGT, weight

TABLE 6 Subgroup analyses according to implant- or restoration-related characteristics and sensitivity analyses according to the study design of the included studies

	Implant failure				Marginal bone loss			
	n	RR	95% CI	P_{SG}	*n*	MD	95% CI	P_{SG}
Subgroup analyses								
3 years follow-up	4	2.45	0.63 to 9.57	0.13	7	0.05 mm	−0.03 to 0.13 mm	0.62
5 years follow-up	4	0.91	0.67 to 1.23		9	0.01 mm	−0.09 to 0.12 mm	
Maxillary implants[a]	7	5.00	0.25 to 100.36	0.18	10	0.03 mm	−0.05 to 0.11 mm	0.98
Mandibular implants[a]	1	0.93	0.68 to 1.25		5	0 mm	−0.11 to 0.12 mm	
Full-arch	3	0.83	0.17 to 4.10	0.85	4	0.01 mm	−0.24 to 0.27 mm	0.30
Partial restorations	5	0.96	0.70 to 1.30		12	0.03 mm	−0.03 to 0.08 mm	
Immediate loading	5	0.95	0.70 to 1.28	0.17	3	0.04 mm	−0.04 to 0.12 mm	0.96
Delayed loading	1	0.19	0.01 to 3.63		12	0.03 mm	−0.05 to 0.12 mm	
Sensitivity analyses								
Retrospective studies	3	0.89	0.65 to 1.21	0.08[b]	8	0.04 mm	−0.04 to 0.11 mm	0.21
Prospective studies	5	2.60	0.77 to 8.79		8	0.04 mm	−0.06 to 0.14 mm	
Large studies	2	0.92	0.67 to 1.25	0.30	6	0.02 mm	−0.04 to 0.09 mm	0.99
Not large studies	6	1.58	0.51 to 4.91		10	0.04 mm	−0.06 to 0.14 mm	

Notes.. CI, confidence interval; MD, mean difference; *n*, number of studies; P_{SG}, *p* value for differences between subgroups/subsets.
[a]Including two trial arms from any studies reporting separate data for both maxilla and mandible.
[b]Statistically significant differences between subsets.

implant" might contain implants with a wide variety of inclinations, which can range (based on the included studies) from 15° to 90°. It is sensible to assume that not all tilted implants might have similar prognosis. This is corroborated from the re-analysis of the raw data from an identified study that indicated that implant angulation is directly associated with measured MBL (Appendix S5). Therefore, future clinical trials should completely report the precise angulation of each implant and assess its effect on prognosis through subgroup analyses.

The frequency of other biological complications pertaining to the health of peri-implant soft tissue conditions like peri-implant mucositis and peri-implantitis was unfortunately not adequately reported in a consistent way. Therefore, differences between tilted and straight implants could not be robustly assessed.

As far as technical complications and PROMs are concerned, only limited data from a few studies existed, which precluded any conclusive statements. It should be however noted that such outcomes usually are measured on the patient or restoration level, such as the acrylic fracture reported in 17% of restorations (Francetti et al., 2012). This, in turn, means that to provide reliable data, randomized controlled trials including only restorations supported by either straight or tilted implants are needed. The combination of tilted and straight implants within the same restoration might introduce confounding factors.

At last, it is important to note that no relevant randomized trial was identified in the literature and only nonrandomized studies were included, which have been shown to be more biased than randomized ones (Papageorgiou et al., 2015,2015a). Furthermore, half of the included studies were retrospective, which have been shown to be more biased than prospective nonrandomized studies (Papageorgiou et al., 2015). Empirical signs of bias originating from retrospective study designs were actually seen in the meta-analysis of implant failure of the present review; compared to straight implants, tilted implants were found to have lower failure risk from retrospective studies, but higher failure risk from prospective studies (p < 0.10; Table 6). Therefore, more prospective studies are needed, so that future systematic reviews can limit their search to prospective studies and robustly assess the survival of tilted implants.

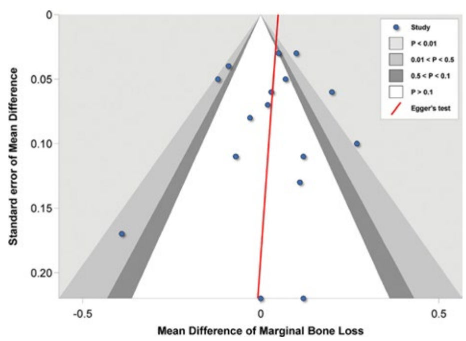

FIGURE 5 Contour-enhanced funnel plot and Egger's test for differences in peri-implant marginal bone loss between tilted and axial implants

4.2 | Strengths, limitations and generalizability

The strengths of this systematic review consist of the registration of its a priori protocol in PROSPERO (Sideri et al., 2018), its exhaustive literature search, its improved analytical methods (Veroniki et al., 2016), the use of the GRADE approach (Guyatt et al., 2008) to assess the quality of the meta-evidence, and its open data-sharing (Naudet et al., 2018).

However, certain limitations also exist. First and foremost, this systematic review included only nonrandomized trials that are at higher risk of bias than randomized ones (Papageorgiou et al., 2015a). As the scope of the review pertained more to adverse effects and diagnosis, nonrandomized designs might be applicable, but half of included studies (53%) were retrospective and therefore at higher risk of bias than prospective studies (Papageorgiou et al., 2015). Also, as both tilted and straight implants were placed and compared within a patient's mouth, analysis was performed on implant level, which ignores clustering effects and might lead to information loss (Altman & Bland, 1997). In addition, methodological issues existed for all included studies, as has been often reported for clinical trials in prosthodontics and implant dentistry (Papageorgiou,

TABLE 7 Summary of findings table according to the GRADE approach

Outcome Trials (patients)	Relative effects (95% CI)	Anticipated absolute effects			Quality of the evidence (GRADE)	What happens
		Straight implants	Tilted implants	Difference (95% CI)		
Implant failure Mean follow-up of 3–5 years 8 studies (4,436 implants)	RR 0.95 (0.70 to 1.28)	2.5% on average	2.4% (1.8 to 3.2)	0.1% fewer implants (0.7 fewer to 1.7 more)	⊕⊖⊖⊖ very low due to bias, imprecision	Little to no difference in implant failure
Peri-implant marginal bone loss Mean follow-up of 3–5 years 16 studies (5,293 implants)	–	1.27 mm MBL on average	–	0.03 mm less MBL (0.03 mm less to 0.10 mm more)	⊕⊖⊖⊖ very low due to bias, inconsistency	Little to no difference in MBL

Notes.. Implant failure and radiographically assessed marginal bone loss around tilted and straight implants. Patient or population: adult patients receiving partial or full dentures supported by tilted and straight implants. Settings: university clinics & private practices (Austria, Belgium, China, Israel, Italy, Portugal, Spain).

CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; MBL, marginal bone loss; RR, relative risk.

[a]Response is based on random-effects meta-analytical pooling of the corresponding straight implant groups among included studies. [b]GRADE for both randomized and nonrandomized studies starts from "high." [c]Downgraded initially to "low" due to the lack of randomization; further downgraded to "very low" due to lack of blinding and further methodological issues. [d]Downgraded further due to imprecision (all studies but one have extremely wide-ranging CIs). [e]Downgraded further due to inconsistency originating (moderate to high inconsistency and wide scattering of studies on both sides of the forest plot).

Kloukos, Petridis, Pandis, 2015b), and these might have influenced the review's results. At last, the identified studies were predominantly small and this might introduce small-study effects (Cappelleri et al., 1996).

The results of the present review are applicable to the average adult patient with partial or total edentulousness of either jaw and treated with partial or full-arch restorations supported by tilted and straight implants in private practices or university clinics.

4.3 | Concluding remarks

In conclusion, besides heterogeneity and the serious risk of bias of most of the studies selected, the present systematic review demonstrated by means of meta-analysis that implant inclination had no effect on peri-implant bone loss or implant survival. Likewise, the assessment of biological and technical complications could not be extracted from the data due to lack of accurate reporting and study design.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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